IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Jack Wands and Jens Encke

Confirmation No.: 3498

Serial No.: 09/600,493

Group Art Unit: 1632

Filing Date: July 18, 2000

Examiner: R. Shukla

For: GENETIC IMMUNIZATION WITH NONSTRUCTURAL PROTEINS OF HEPATITIS C VIRUS

Considered RRS 2/25/03

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

DECLARATION OF DR. JACK R. WANDS UNDER 37 C.F.R. § 1.132

I, Jack R. Wands, state as follows:

1. I am a co-inventor of the above-captioned patent application ("the subject application").

2. I have reviewed the Office Action dated September 24, 2002. As I understand it, the examiner has suggested that, for various reasons, the present invention is not enabled by the specification.

3. This declaration is provided to demonstrate that practice of the claimed recombinant nucleic acid molecule, pharmaceutical composition, method of inducing an immune response against hepatitis C in a human, and method of treating a human who is infected with hepatitis C virus is fully enabled by the specification.

4. The subject application provides ample detail to enable one skilled in the art to construct a recombinant nucleic acid molecule comprising a nucleotide sequence encoding hepatitis C virus nonstructural protein, for example, NS3, NS4 or NS5 protein, wherein said nucleotide sequence is operably linked to a promoter, enhancer, polyadenylation sequence, and 5' untranslated region (5'-UTR) of hepatitis C virus. The subject application further provides ample detail to produce a pharmaceutical composition or to practice a method of inducing an immune response using the recombinant nucleic acid molecule.

5. Utilizing information provided in the subject application, one skilled in the art can construct a recombinant nucleic acid molecule encoding hepatitis C virus nonstructural protein, for example, NS3, NS4 or NS5 protein, as taught in the specification, for example, page 15, l. 22 to page 16, l. 17, operably linked to a promoter, enhancer, and polyadenylation sequence as taught in the specification, for example, page 11, l. 3 to page 12, l. 7, and further operably linked to a 5'-untranslated region of hepatitis C virus as taught in the specification, for example, page 10, l. 26 to page 11, l.2, and page 10, l. 18-26.

6. Utilizing information provided in the subject application and in Yoo et al. *Virology* **191**: 889-899, 1992, one skilled in the art would understand the function of the 5' UTR of hepatitis C virus, including the positive and negative translational control elements within the 5'-UTR. One skilled in the art would be able to operably link the 5'UTR of hepatitis C virus to a recombinant nucleic acid molecule acting as an expression plasmid for proteins, for example, hepatitis C virus non-structural (NS) protein.

7. Utilizing information provided in the subject application, as detailed in paragraph 5 and, for example, in Example 1 of the specification, "Design of HCV expression vectors," and using molecular biological techniques known in the art at the time of filing the application, one skilled in the art would be able to construct a recombinant nucleic acid molecule comprising a nucleotide sequence

encoding hepatitis C virus nonstructural protein, for example, NS3, NS4 or NS5 protein, wherein said nucleotide sequence is operably linked to a promoter, enhancer, polyadenylation sequence, and 5' untranslated region (5'-UTR) of hepatitis C virus.

8. I am a co-author of the publications by Tokushige et al., *Hepatology* **24**: 14-20, 1996 and Encke, et al. *J. Immunol.* **161**: 4917-4923, 1998. The results shown in Examples 1 through 7 of the subject application taken with results shown in Tokushige et al. and Encke, et al. enable one skilled in the art to conclude that immunization of a human with a pharmaceutical composition comprising a recombinant nucleic acid molecule comprising a nucleotide sequence encoding hepatitis C virus nonstructural protein, for example, NS3, NS4 or NS5 protein, wherein said nucleotide sequence is operably linked to a promoter, enhancer, polyadenylation sequence, and 5' untranslated region (5'-UTR) of hepatitis C virus would stimulate a strong humoral immune response and a strong specific $CD8^+$ cytotoxic T-cell (CTL) response.

9. In support of the facts of paragraph 8, a skilled person will appreciate that non-structural (NS) proteins are better than core proteins as antigens to stimulate a cell-mediated and humoral immune response. See specification, for example, page 14, l. 21-27, and Example 4, page 19; and Encke et al., page 4922.

10. In further support of the facts of paragraph 8, it will be seen that strong specific $CD8^+$ cytotoxic T-cell (CTL) response and *in vivo* CTL activity in a mouse tumor model is generated for recombinant nucleic acid molecules expressing non-structural (NS) proteins, for example, NS3 and NS5. See specification, for example, p. 15, l. 1-5, and Examples 4 to 7, pages 19 to 23; and Encke et al., Figures 3 and 4, pages 4921-4922.

11. A scientist of ordinary skill following the teachings of the subject application would have found sufficient guidance to construct a recombinant nucleic acid molecule comprising a nucleotide sequence encoding hepatitis C virus nonstructural protein, for example, NS3, NS4 or NS5 protein, wherein said nucleotide sequence is operably linked to a promoter, enhancer, polyadenylation sequence, and 5' untranslated region (5'-UTR) of hepatitis C virus. The results summarized in paragraphs 5, 6, and 7, above, demonstrate a recombinant nucleic acid molecule as claimed in the subject application.

12. A scientist of ordinary skill following the teachings of the subject application would have found sufficient guidance to make a pharmaceutical composition or a method of inducing an immune response using the recombinant nucleic acid molecule as claimed in the subject application and to use the composition or method to generate a humoral immune response and a specific $CD8^+$ cytotoxic T-cell (CTL) response in animals other than mice using the teachings of the subject application. The results summarized in paragraphs 8 through 10, above, demonstrate a pharmaceutical composition or a method of inducing an immune response using the recombinant nucleic acid molecule as claimed in the subject application.

13. A scientist of ordinary skill following the teachings of the subject application would have found sufficient guidance to extrapolate the methods used in mouse to other animals in order to induce an immune response in other animals, for example, humans, considering the state of the art of DNA based immunization, mouse as an animal model for HCV, and the role of the 5'-UTR of hepatitis C virus in regulation of gene expression. The results summarized in paragraphs 8 through 10, above, are accepted by one skilled in the art as a model to demonstrate a pharmaceutical composition and a method of inducing an immune response against hepatitis C in a human, and a method of treating a human who is infected with hepatitis C virus using the recombinant nucleic acid molecule as claimed in the subject application.

14. I further declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that any such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 11/23/03

Jack R. Wands, M.D.